Characteristics of Choroidal Neovascularization in the Complications of Age-Related Macular Degeneration Prevention Trial

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Objective: To describe the characteristics of incident choroidal neovascularization (CNV) in observed and treated eyes in the Complications of Age-related Macular Degeneration Prevention Trial (CAPT).

Design: Cross-sectional descriptive study within a multicenter, randomized clinical trial.

Participants: Patients who developed CNV during CAPT follow-up.

Methods: Inclusion criteria for CAPT specified bilateral large drusen (≥10 drusen at least 125 μ), visual acuity ≥20/40 in each eye, and age ≥50. Exclusion criteria included CNV and geographic atrophy >1 Macular Photocoagulation Study (MPS) disc area or within 500 μ of the foveal center. One eye of each person was selected randomly for low-intensity laser treatment and the contralateral eye was observed. Fluorescein angiography was performed at baseline, annually for ≥5 years, and whenever there were symptoms of CNV. Trained readers at the CAPT Photograph Reading Center assessed color stereo photographs and angiogram negatives to identify CNV.

Main Outcome Measures: Choroidal neovascularization was classified by type (predominantly classic CNV, minimally classic CNV, occult only CNV, or scar), location, and area. Visual acuity was measured by certified examiners. Symmetry of characteristics between eyes of bilaterally affected patients was examined.

Results: Choroidal neovascularization developed in 282 eyes of 225 patients. At the time of detection, 192 (68%) of the lesions were occult only, 153 (54%) were subfoveal, and 157 (56%) were ≤2 MPS disc areas. Visual acuity was ≥20/40 in 123 (69%) of 179 eyes with visual acuity measured at the time of detection. Choroidal neovascularization developed in both eyes in 57 patients (25%) during CAPT follow-up. Lesions in eyes of bilaterally affected patients were no more similar to each other than affected eyes in 2 different patients.

Conclusions: When patients are monitored closely, many CNV lesions can be detected outside of the fovea and when they are relatively small. Early detection may lead to improved long-term visual acuity.

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The Complications of Age-related Macular Degeneration Prevention Trial (CAPT) was a multicenter, randomized clinical trial sponsored by the National Eye Institute to evaluate low-intensity laser treatment for the prevention of vision loss from age-related macular degeneration in patients with bilateral large drusen. The CAPT was conducted at 22 clinical centers involving 1052 participants. Participants had ≥10 large drusen and visual acuity of ≥20/40 in each eye and were followed for ≥5 years after laser treatment. Previously published results of this study showed no evidence of a clinically significant beneficial, or harmful, effect of the CAPT laser treatment.[1] The proportions of eyes with development of ≥3 lines of loss of visual acuity, with choroidal neovascularization (CNV), and with geographic atrophy were nearly equal in the 2 treatment groups.

The CAPT provided the opportunity to describe incident CNV among a well-defined group of patients. Previous case series of CNV have been from tertiary referral centers and may not be representative of incident CNV.[2–9] We report herein on the characteristics of incident CNV in the treated and observed eyes in patients enrolled in CAPT.

Methods

Overview of the Clinical Trial

Details of the design of CAPT appear elsewhere.[10,11] The features relevant to this report are addressed here. A total of 1052 participants were enrolled at 22 centers between May 1999 and March 2001. Each center had approval from its local institutional review

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board to conduct the study and for use of a written consent form. Both eyes of each participant were enrolled. The CAPT eligibility criteria required that each eye have ≥10 large drusen (≥125 μ in diameter) within 3000 μ of the center of the macula and visual acuity ≥20/40. Neither eye could have evidence of CNV, serous retinal pigment epithelium detachment (SPED), geographic atrophy >1 macular photocoagulation study (MPS) disc area in size, geographic atrophy of any size within 500 μ of the foveal center, or any condition likely to affect visual acuity within the next 5 years.

One eye of each patient was assigned randomly to low-intensity laser treatment, and the other eye was assigned to observation. Initial treatment consisted of 60 barely visible burns in a grid pattern using a 100-μ spot size delivered for 0.1-second duration. Treatment was applied within an annulus between 1500 and 2500 μ from the foveal center. Fifteen burns were applied per quadrant without regard to drusen (i.e., no effort was made to hit or avoid drusen). Argon green (514 nm) was the preferred wavelength; however, other wavelengths could be used if an argon green laser was not available.

Twelve months after the initial treatment session, additional treatment was performed if ≥10 drusen with >125 μ diameter (or an equivalent area) remained within 1500 μ of the foveal center. When the retreatment criteria were met, 30 burns were administered in the annulus between 1000 and 2000 μ from the foveal center. Drusen were targeted for direct application of laser burns. If all drusen within the annulus could be treated with fewer than 30 burns, the remainder of the burns was applied evenly within the treatment annulus.

Patients were scheduled for examinations at 6 months and then annually for either 5 or 6 years of follow-up, depending on the date of enrollment. Patients were examined annually and at 6 months after enrollment. Visual acuity was measured on Early Treatment Diabetic Retinopathy Study charts by certified examiners using a standard protocol. Visual acuity examiners were masked to treatment assignment. Patients with CNV detected during an unscheduled examination did not have visual acuity recorded.

Photography

Color stereoscopic 30-degree photographs centered on the disc and centered on the macula were obtained of both eyes at baseline. At annual visits and at 6 months, color stereoscopic photographs centered on the macula were obtained. A stereoscopic 30-degree fluorescein angiogram was obtained at baseline and annual visits. The angiography protocol included both eyes during the early phase. The angiography protocol specifically included stereoscopic pairs of the right eye at 20 to 35, 70 to 75, 90, and 130 to 140 seconds and at 3, 5.5 to 6, and 10 minutes. The protocol for the left eye included stereoscopic pairs at 45 to 50, 60, 100 to 110, and 120 seconds and at 3.5 to 4, 5 to 5.5, and 10 minutes. Stereoscopic pairs of both discs were obtained at 5 to 6 minutes.

Patients who recognized and reported symptoms between regularly scheduled examinations were seen by a CAPT ophthalmologist. Fluorescein angiography and color photography were performed when CNV or SPED was suspected by the ophthalmologist.

Photograph Reading

All photographic images described above were graded independently by 2 trained readers in the CAPT Reading Center. The readers openly discussed their discrepancies to arrive at consensus. Unresolved differences were reviewed by either the Reading Center director or principal investigator (an ophthalmologist). All new CNV and SPEDs identified by the readers were reviewed by the principal investigator.

Choroidal neovascularization was considered present when there was expansion or persistent staining of an area of hyperfluorescence as the time increased from injection of dye on fluorescein angiography. A SPED was considered present when there was a uniform, smooth elevation of the retinal pigment epithelium with sharply demarcated, fairly uniform, early hyperfluorescence that persisted into the late phase of the angiogram.

The CAPT ophthalmologists completed case report forms when they first detected CNV or SPED on a patient's photographs. If the Reading Center staff detected CNV or SPED and the CAPT ophthalmologist had not, the ophthalmologist was notified and asked to review the photographs for the presence of CNV or SPED. The ophthalmologist reported the interpretation to the Reading Center after the review. The interpretation by the Reading Center staff was used for the analyses in this paper.

Readers graded the lesion composition, location, and size. Classic CNV was graded as present when there was an area of choroidal hyperfluorescence with well-demarcated boundaries that could be discerned in the early phase of the angiogram. In later phases of the angiogram, there was progressive pooling of dye leakage in the overlying subsensory retinal space that usually obscures the boundaries of the CNV. Occult CNV was graded as present when an area of stippled hyperfluorescence appeared within 5 minutes of fluorescein injection with persistent staining or pooling of dye in the overlying subsensory retinal space by 10 minutes. The CNV component of a lesion was classified as <50% or ≥50% classic CNV. Blood contiguous with the CNV was classified as less than the area of the CNV or equal to or greater than the area of the CNV. The location of the lesion was identified as subfoveal (under the foveal center), peripapillary (adjacent to the optic disc), or neither subfoveal nor peripapillary. Lesions that were >3000 μ from the foveal center were excluded from the grading. The size of the total lesion (classic CNV, occult CNV, contiguous blood, scar, and SPED) was graded in categories ranging from ≤1 MPS disc area, to >12 MPS disc areas.

Assessment of Reproducibility in Grading

A weighted sample of eyes with and without CNV or SPED was selected for regrading. All photographic images were regraded independently by 2 readers who later openly discussed their discrepancies to arrive at consensus. Unresolved differences were reviewed by either the Reading Center director or principal investigator (an ophthalmologist). All new CNV and SPEDs identified by the readers were reviewed by the principal investigator.

Data Analysis

Data received by the CAPT Coordinating Center by June 30, 2006, are included in this report. Agreement among readers and over time was evaluated with the weighted kappa statistic and with the percent agreement. Comparisons of the characteristics of CNV lesions between treated and observed eyes were evaluated with chi-square tests, with adjustment for the correlation between eyes of the same person when CNV was present in both eyes.[12] Correlation of lesion characteristics in 2 eyes of the same person was summarized with the percent concordance and assessed with chi-square tests of independence. Only visual acuity measurements taken during the visit when the CNV was first recognized are included in the analysis of visual acuity. Visual acuity was not measured under protocol conditions when patients had their CNV detected between regularly scheduled CAPT visits.

Results

Reproducibility Results

The percent agreement of angiographic evidence of CNV or SPED was excellent (93.8%–100%) with substantial kappa values (0.64–0.86). For lesion components (CNV type, blood, scar, SPED) agreement also was excellent (80%–100%) with substantial weighted kappa values (0.75–1.00).

Choroidal Neovascularization Characteristics

Choroidal neovascularization developed in 141 treated eyes and in 141 observed eyes. In addition, SPED, in the absence of apparent CNV, developed in 2 treated eyes and 5 observed eyes. Only eyes with CNV are described in the remainder of this report.

The distributions of CNV characteristics in treated and observed eyes are displayed in Table 1. Differences between treatment groups were not statistically significant for lesion type, location, size, or presence of SPED. Classic CNV only was present in 43 (15.2%) of 282 eyes, and occult CNV only was present in 192 (68.1%) eyes. Both types of CNV were present in 33 (11.7%) eyes and among those eyes classic CNV was ≥50% of entire area of CNV in 10 (30.3%) eyes. The first presentation of CNV within CAPT was a scar only in 1 eye; this eye had been treated outside of CAPT with photodynamic therapy 11 months earlier between CAPT examinations. More than half (153; 54.3%) of the 282 eyes had subfoveal lesions and more than half (157; 55.7%) were ≤2 MPS disc areas. In addition to CNV, SPED was present in 17 (6%) eyes. Blood was present in more treated eyes (73 of 141 [51.8%]) than observed eyes (53 of 141 [37.6%]; $P = 0.01$).

Visual Acuity

Visual acuity and loss of visual acuity from baseline were similar in 179 treated and observed eyes that had protocol visual acuity measurements reported from the visit when CNV was first detected (Table 2). Visual acuity was not reported when CNV was detected during an unscheduled visit. Among the 179 eyes, 123 (68.7%) had visual acuity of ≥20/40. When only the 87 eyes with subfoveal CNV were considered, 44 (50.6%) had visual acuity of ≥20/40. Most eyes (127 of 179; 70.9%) had lost ≤2 lines from their baseline measurement (Figure 1).

Symmetry of Choroidal Neovascularization

There were 225 patients who developed CNV during CAPT, 57 of whom (25%) developed CNV in both the treated and observed eyes. Overall, CNV lesions in the 2 eyes of a patient were no more similar to each other than 2 eyes from different patients with respect to lesion composition, location, and size ($P \geq 0.10$). For example, among 56 patients with lesion location known for each eye, 50% of the treated eyes and 56% of the observed eyes had subfoveal lesions. The lesions were subfoveal in both eyes of 18 of the patients (32%), only slightly more than would be expected (15.5 patients or 28% of the 56 patients) if there were no correlation in lesion location between the 2 eyes of

Table 1. Characteristics of Choroidal Neovascular Lesions at First Presentation

	Treated (N = 141)			Observed (N =141)		All (N = 282)	
	N	*Percent*		*N*	*Percent*	*N*	*Percent*
Type of choroidal neovascularization							
Classic only	23	(16.3)		20	(14.2)	43	(15.2)
Occult only	94	(66.7)		98	(69.5)	192	(68.1)
Classic and occult	17	(12.1)		16	(11.3)	33	(11.7)
Disciform scar only	0	(0.0)		1	(0.7)	1	(0.4)
Cannot determine type/cannot grade	7	(5.0)		6	(4.3)	13	(4.6)
P value*			0.63				
Lesion location							
Subfoveal	76	(53.9)		77	(54.6)	153	(54.3)
Neither subfoveal nor peripapillary	62	(44.0)		61	(43.3)	123	(43.6)
Peripapillary	2	(1.4)		3	(2.1)	5	(1.8)
Cannot determine	1	(0.7)		0	(0.0)	1	(0.4)
P value*			1.00				
Size of lesion (disc areas)							
≤1	53	(37.6)		49	(34.8)	102	(36.2)
1<*x*≤2	31	(22.0)		24	(17.0)	55	(19.5)
2<*x*≤3.5	29	(20.6)		28	(19.9)	57	(20.2)
>3.5	20	(14.2)		32	(22.7)	52	(18.4)
Cannot determine/grade	8	(5.7)		8	(5.7)	16	(5.7)
P value*			0.16				
Contiguous blood							
Present	73	(51.8)		53	(37.6)	126	(44.7)
Absent	66	(46.8)		86	(61.0)	152	(53.9)
Cannot grade	2	(1.4)		2	(1.4)	4	(1.4)
P value*			0.01				
Serous PED							
Present	6	(4.3)		11	(7.8)	17	(6.0)
Absent	135	(95.7)		130	(92.2)	265	(94.0)
P value*			0.16				

PED = pigment epithelium detachment.
*Eyes classified as cannot grade or cannot determine were excluded from the calculations.

Table 2. Visual Acuity of Eyes at First Presentation of Choroidal Neovascularization

	Treated (N = 93)		Observed (N = 86)		All (N = 179)	
Visual Acuity	*N*	*Percent*	*N*	*Percent*	*N*	*Percent*
20/12 to 20/40	64	(68.8)	59	(68.6)	123	(68.7)
20/50 to 20/160	26	(28.0)	22	(25.6)	48	(26.8)
20/200 to <20/400	3	(3.2)	5	(5.8)	8	(4.5)

the same patient. Similar calculations for lesion composition yield 26.5 patients expected to have occult only lesions in each eye with 28 patients actually having occult only lesions in each eye.

Association of Choroidal Neovascularization with Laser Burns

The photographs of 23 patients who developed classic only CNV lesions in their treated eye (Table 1) were examined by one of the authors (JA) to identify eyes that had CNV develop in the area of laser treatment. A second author (SLF) reviewed the subset of 7 eyes that developed CNV in the area of treatment. There was 1 eye with CNV detected 9 months after the initial treatment in which the neovascularization appeared to emanate from a visible treatment burn.

Discussion

The data from CAPT provide unique information on the angiographic characteristics of incident CNV among patients who were followed at regular intervals for 5 or 6 years. Previous reports on the characteristics of CNV have been from tertiary referral centers subject to selection factors and time lags after onset. A variety of selection factors may skew the characteristics of referral patients, ranging

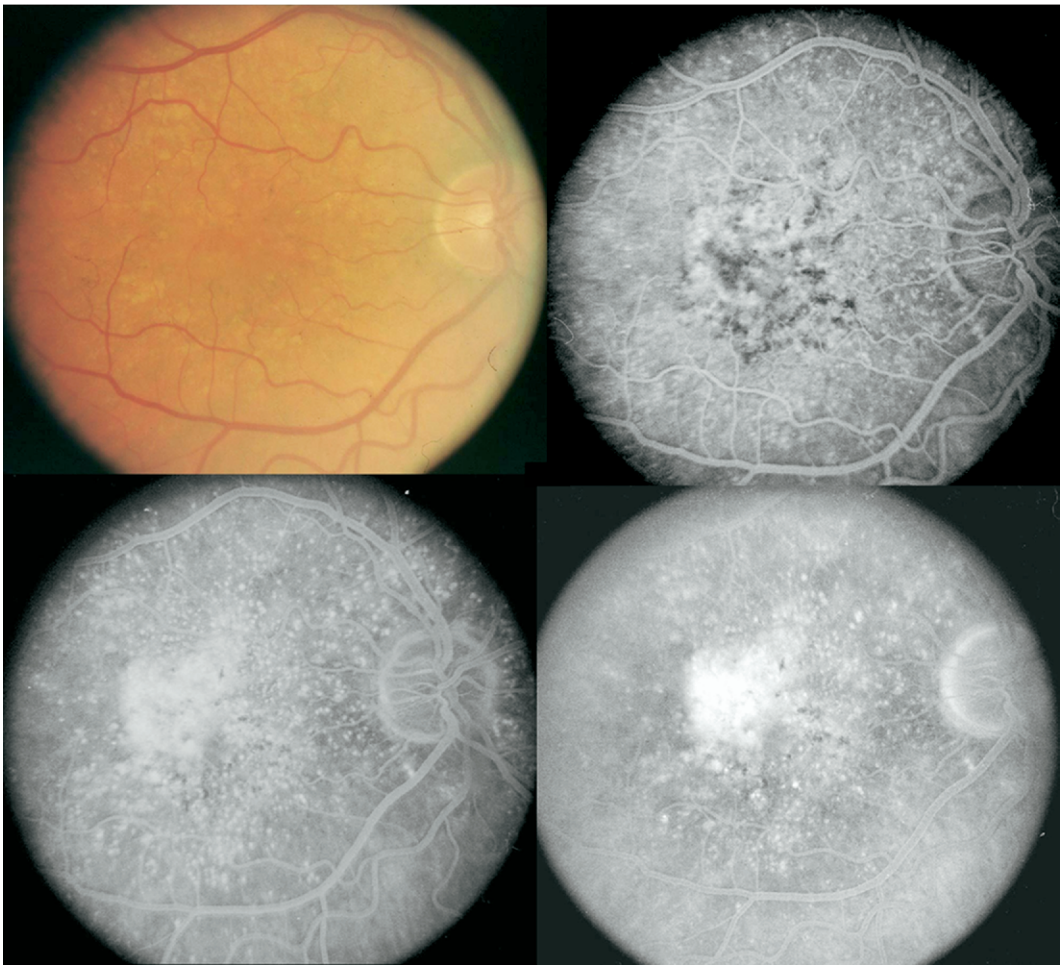

Figure 1. Subfoveal, predominantly occult, choroidal neovascularization in an eye with 20/25 visual acuity 2 years after study entry. Visual acuity at entry was 20/20. Upper left, Color photograph. Upper right, Frame from the early phase of fluorescein angiography (FA). Lower left, Frame from midphase of FA. Lower right, Frame from late phase of FA.

from nonreferral of patients with lesions clearly amenable to the treatments widely available at the time to nonreferral of patients with very large lesions and low visual acuity for whom treatment might be futile. Follow-up in CAPT was nearly complete, so that the CNV observed in CAPT was representative of patients who enrolled. However, the features of CNV developing in the CAPT patients who had many large drusen bilaterally may not be representative of CNV that develops in eyes with few and/or only smaller drusen. It is possible that the CAPT low-intensity preventive treatment could influence the characteristics of subsequent CNV, but the characteristics of CNV in the treated eyes was remarkably similar to the characteristics in the untreated eyes (Table 1). In addition, among the 141 treated eyes, there was only 1 eye (0.7%) that had clear signs of CNV emanating from a treatment burn. However, an association between laser treatment and CNV could not be determined in most eyes because (1) most neovascular lesions had occult CNV without a clear source of fluorescein leakage; (2) many treatment burns were not detectable on the immediate posttreatment color photographs or subsequent angiograms; and (3) the retinal area intended for initial treatment (1500–2500 μ from the foveal center) or retreatment (1000–2000 μ from the foveal center) was frequently the site of CNV in both untreated eyes and treated eyes.

Annual fluorescein angiography, which is not standard practice for patients with bilateral drusen, likely contributed to identification of CNV earlier in CAPT than in other reports of case series. The proportion of CNV lesions that were subfoveal at presentation was lower in CAPT (153 of 282; 54%) than in studies reported by Freund et al[5] (50 of 65; 77%), Moisseiev et al[6] (44 of 63; 70%), Gelfand et al[7] (35 of 50; 70%), Margherio et al[8] (393 of 474; 83%), and Cohen et al[9] (166 of 205; 81%).[5–9] Only 15% of the CNV lesions detected in CAPT consisted of only classic CNV and more than half were ≤2 MPS disc areas. It is therefore not surprising that visual acuity was relatively good in most eyes (Table 2). Among the 179 eyes with measurements taken at the time of detection of CNV, visual acuity was ≥20/40 in 123 (69%). Approximately 100 of the cases of CNV were detected between regularly scheduled examinations when patients reported symptoms or their ophthalmologist wanted to see the patient more frequently than annually. Visual acuity was not measured at these unscheduled examinations. Visual acuity in these 100 eyes with newly detected CNV may have been worse than in eyes in which the CNV was detected at a regularly scheduled examination.

Close monitoring of high-risk eyes, such as fellow eyes in patients with unilateral CNV or eyes with multiple large drusen and pigmentary changes, can lead to detection of CNV when it is more likely to be outside the fovea, relatively small, and without a large loss in visual acuity. Regular retinal examinations, optical coherence tomography, preferential hyperacuity perimetry, and use of the Amsler grid may aid in early detection of CNV.[13] Interestingly, the Phase III trials of photodynamic therapy and anti-vascular endothelial growth factor agents have excluded patients with visual acuity >20/40 and with lesions outside the fovea so that most of the CNV detected in CAPT would not have been eligible for these trials.[14–18] If the results of these trials can be extrapolated, early detection and treatment of lesions before loss of substantial visual acuity should provide patients with the best chance of maintaining good visual acuity. Future studies should be performed to determine the long-term outcome of application of these treatments to eyes with visual acuity >20/40 and lesions outside the fovea.

Bilateral involvement is common in neovascular age-related macular degeneration, with approximately 10% of second eyes developing CNV each year through at least the first 5 years after development of CNV in the first eye.[19,20] There have been few studies of the symmetry of CNV lesions. Lavin et al[21] noted modest correlation ($r = 0.5$) between the final size of disciform scars in bilaterally affected patients. Pauleikhoff et al[22] classified lesions as either CNV ("angiographically visible predominantly classic CNV without serous pigment epithelium detachments [SPED]") or PED ("occult CNV and associated SPED") and found nearly perfect symmetry on this feature between the lesions in the eyes of 53 patients. In CAPT, there was little evidence that more patients are affected bilaterally with occult CNV only than would be expected by the overall prevalence of this type of lesion.

In conclusion, CNV in eyes of patients followed within the CAPT were less likely to be subfoveal than in other previously reported case series. Many eyes with CNV were detected before the loss of substantial visual acuity. Regular monitoring of high-risk patients may allow early detection and treatment that may result in long-term preservation of visual acuity.

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